REMARKS

Claims 1-2 are pending in this application. Claim 1-2 have been rejected and amended. Claims 6 and 7 have been added. No new matter has been added. Applicants are respectfully requesting reconsideration of the restriction requirement in view of the following remarks.

I. Priority

The amendments to the specification filed on February 15, 2005 have been objected to because the incorporation of priority documents by reference is inappropriate. Applicants have made the appropriate amendment to the specification and respectfully request that this rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. §112

The rejection of claims 1-2 under 35 U.S.C. 112, first paragraph, has been maintained. The Examiner suggests that the art supports the unpredictability of the broadly drawn claims as Matsumura et al. ((2004) *J. Cancer Res. Clin. Oncol.* 130:259-265); Przybylowska et al. ((2002) *Exper. Oncol.* 24:25-27); Wenham et al. ((2003) *J. Soc. Gynecol. Invest.* 10:381-7); Lai et al. ((2005) *Gynecol. Oncol.* 96:314-9); Ju et al. ((2005) *Cancer Lett.* 217:191-196) teach that the 1G/2G polymorphism is not associated with gastric cancer, colorectal cancer, ovarian cancer, HSIL/SCC or cervical cancer, respectively. Further, the Examiner suggests that ethnic differences in the genotype distribution of the MMP-1 promoter exist in rheumatoid arthritis patients (Lee et al. (2003) *Scand. J. Rheumatol.* 32:235-239). It is further that the A2058 tumor cell lines disclosed in the instant specification are

not an appropriate means for examining associations with diseases because Sidransky et al. (U.S. Patent No. 5,856,094) and Teng et al. (U.S. Patent No. 5,989,885) teach that mutations in cell lines are not indicative of primary tumors. Moreover, it is suggested that because the occurrence if 2G homozygotes in the CEPH controls was determined to be ~30% and the tumor cell lines was 62.5%, the skilled artisan would incorrectly diagnose a patient with a MMP-1 disease 30% of the time. The Examiner suggests that the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. Applicants respectfully disagree.

The teachings of Matsumura et al., Przybylowska et al., Wenham et al., Lai et al., and Ju et al. focus on the 1G/2G MMP-1 polymorphism in gastric cancer, colorectal cancer, ovarian cancer, HSIL/SCC or cervical cancer. Lee et al. focus on genotype distribution of the MMP-1 promoter in rheumatoid arthritis patients. Sidransky et al. and Teng et al. focus on correlations between homozygous deletions in breast cancer cell lines and the presence of homozygous deletions or point mutations in primary breast carcinomas. These references are silent with respect to melanoma cancer. In contrast, the instant specification teaches that a direct correlation exists between the overexpression of MMP-1 in a melanoma cell and a 5'-AAGAT-3' to 5'-AAGGAT-3' Ets transcription factor binding site single nucleotide polymorphism in the MMP-1 promoter sequence (page 5, lines 4-23). Thus, in an effort to clarify the instant teachings, Applicants have amended claims 1 and 2 to clarify that the 5'-AAGAT-3' to 5'-AAGGAT-3' Ets transcription factor binding site SNP in the MMP-1 promoter

sequence is used in the diagnosis or prognosis of melanoma cancer.

As indicated in Applicants response filed February 15, 2005, the A2058 human melanoma cell line employed in the instant invention is well-known in the art for being highly representative of human melanoma *in vivo*. For example, Wang et al. ((1988) *Cancer Res.* 48:6262-71; abstract enclosed herewith) teach that invasion by A2058 melanoma cells lines is inhibited by estramustine. Bjork et al. ((1991) *Anticancer Res.* 11:1173-82; abstract enclosed herewith) indicate that this cytotoxic effect, which is also observed *in vivo,* is mediated by the estramustine/estromustine-binding protein in human melanoma. Accordingly, protein expression and drug toxicity of the A2058 cell line are highly correlative with that observed *in vivo* making the A2058 cell line a suitable model system human melanoma. Thus, it is respectfully requested that this rejection be reconsidered and withdrawn.

In an effort to more precisely define certain aspects of the present invention, Applicants have further added claims 6 and 7 drawn to methods for detecting the overexpression of a matrix metalloproteinase-1 or assessing the invasiveness of a tumor cell by detecting in the matrix metalloproteinase-1 promoter sequence comprising SEQ ID NO:6 a 5'-AAGAT-3' to 5'-AAGGAT-3' Ets transcription factor binding site single nucleotide polymorphism. Support for these claims can be found at page 5-10.

Claims 1-2 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner suggests

that it is unclear whether the claims are drawn to detecting SEQ ID NO:6 as indicative of the mutation or whether the claim is drawn to a SEQ ID NO:6 as the promoter sequence. It is suggested that the phrasing of "comprising SEQ ID NO:6" is unclear whether the mutation comprises SEQ ID NO:6 or whether the promoter sequence comprises SEQ ID NO:6. Applicants have amended claims 1 and 2 to clarify that the polymorphism is detected in a promoter comprising SEQ ID NO:6. Withdrawal of this rejection is therefore respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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